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SEARCH REQUEST FORM

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Art Unit 1614 Location (Bldg/Room#): CM1-2A17 Phone (circle 305 306 (308) 4650

Serial Number: 09/177,273 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention Methods and Materials for Treating and Preventing Inflammation of mucosal tissue

Inventors (please provide full names): _____

Jens Ponikau

Earliest Priority Date: 10/22/97

Keywords (include any known synonyms registry numbers, explanation of initialisms):

Antifungal agent is selected from

Amphotericin B	Flucytosine	propionic acid	Whitfield's ointment
Ketoconazole	miconazole	Terconazole	tolnaftate
Itraconazole	fluconazole	Butoconazole	naftifine
saperconazole	griseofulvin	Oxiconazole	terbinafine
voriconazole	clotrimazole	Sulconazole	morpholines
	econazole	Ciclopirox	nystatin
		Olamine	natamycin
		Haloprogin	butenafine
			undecylenic ac

Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

A method for treating intestinal mucositis with an antifungal agent.

Point of Contact:
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STAFF USE ONLY

Searcher: Beverly C 4994

~~Searcher Phone #:~~ _____

Searcher Location: _____

Date Picked Up: _____

Date Completed: 09-15-99

~~Clerical~~ Prep Time: 12

Terminal Time: 9

Number of Databases: 1

Type of Search

_____ N.A. Sequence
_____ A.A. Sequence
_____ Structure (#)
_____ Bibliographic
_____ Litigation1
_____ Fulltext
_____ Procurement
_____ Other

Vendors (include cost where applicable)

__✓__ STN
_____ Questel/Orbit
_____ Lexis/Nexis
_____ WWW/Internet
_____ In-house sequence systems (list)
_____ Dialog
_____ Dr.-Link
_____ Westlaw
_____ Other (specify)

FILE 'REGISTRY' ENTERED AT 16:51:05 ON 10 SEP 1999
L1 17 SEA ABB=ON PLU=ON (PROPIONIC ACID OR TOLNAFTATE OR AMPHOTERICIN B OR FLUCYTOSIN OR TERCONAZOLE OR NAFTIFINE OR KETOCONAZOLE OR MICONAZOLE OR BUTOCONAZOLE OR TERBINAFINE OR ITRACONAZOLE OR FLUCONAZOLE OR OXICONAZOLE OR MORPHOLINE OR SAPERCONZAOLE OR GRISEOFULVIN OR SULCONAZOLE)/CN
E SAPERCONAZOLE/CN 5
L2 1 SEA ABB=ON PLU=ON SAPERCONAZOLE/CN
L3 8 SEA ABB=ON PLU=ON (NYSTATIN OR VORICONAZOLE OR CLOTRIMAZOLE OR CICLOPIROX OR NATAMYCIN OR ECONAZOLE OR HALOPROGIN OR UNDECYLENIC ACID)/CN
L4 26 SEA ABB=ON PLU=ON L1 OR L2 OR L3

FILE 'CAPLUS' ENTERED AT 16:54:20 ON 10 SEP 1999
L5 47630 SEA ABB=ON PLU=ON PROPIONIC ACID OR TOLNAFTATE OR AMPHOTERICIN B OR FLUCYTOSIN OR TERCONAZOLE OR NAFTIFINE OR KETOCONAZOLE OR MICONAZOLE OR BUTOCONAZOLE OR TERBINAFINE OR ITRACONAZOLE OR FLUCONAZOLE OR OXICONAZOLE OR MORPHOLINE OR SAPERCONAZOLE OR GRISEOFULVIN OR SULCONAZOLE
L6 40890 SEA ABB=ON PLU=ON L4 OR NYSTATIN OR VORICONAZOLE OR CLOTRIMAZOLE OR CICLOPIROX OR NATAMYCIN OR ECONAZOLE OR HALOPROGIN OR UNDECYLENIC ACID
L7 10 SEA ABB=ON PLU=ON (L5 OR L6) AND MUCOSIT?

L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1999:312077 CAPLUS
DOCUMENT NUMBER: 130:346876
TITLE: Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma
AUTHOR(S): Schwartz, J. D.; Howard, W.; Scadden, D. T.
CORPORATE SOURCE: New York Hosp./Cornell Med. Center Hematology/Oncology, New York, NY, 10021, USA
SOURCE: AIDS (London) (1999), 13(2), 283-284
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interactions between cytochrome P 450 3A(CYP3A)-suppressive anti-HIV regimens and paclitaxel resulted in substantial chemotherapy-related side effects in patients with AIDS-related Kaposi's sarcoma. Paclitaxel (100 mg/m2) administration over 3 h every other week to patients with HIV infection and Kaposis sarcoma resulted in near-total disappearance of Kaposi's sarcoma. The first 12 cycles were complicated only by mild nausea and alopecia; intermittent granulocyte colony-stimulating factor was used to prevent neutropenia. Antiretroviral therapy included several

combinations of zidovudine, zalcitabine, lamivudine, stavudine, and indinavir, all of which were unsuccessful in reducing the viral load. Subsequently the patients were started on didanosine, saquinavir and delavirdine. As a result of this therapy, paclitaxel resulted in profound **mucositis** requiring hospitalization and febrile neutropenia with an abs. neutrophil count <100 x106/l. Given the above scenario, it is likely, that coadministration of delavirdine and saquinavir results in a situation where levels of either (or both) drugs are increased and concomitant administration of taxane chemotherapy with paclitaxel leads to side-effects significantly out of proportion to the taxane dose used. Thus, taxane doses in these situations should be reduced and patients carefully monitored.

IT **86386-73-4, Fluconazole**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma)

L7 ANSWER 2 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1999:282082 CAPLUS
DOCUMENT NUMBER: 130:306586
TITLE: Methods and materials for treating and preventing inflammation of mucosal tissue using antifungal agents, and diagnostic methods and materials
INVENTOR(S): Ponikau, Jens
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920261	A2	19990429	WO 1998-US22403	19981022

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9911959	A1	19990510	AU 1999-11959	19981022
PRIORITY APPLN. INFO.:			US 1997-62709	19971022
			US 1997-63414	19971028
			US 1997-63418	19971028
			US 1998-83272	19980428
			US 1998-86397	19980522
			WO 1998-US22403	19981022

AB The invention involves methods and materials for treating and preventing non-invasive fungus-induced **mucositis**. Specifically, the invention involves administering an antifungal agent such that it contacts mucus in an amt., at a frequency, and for a duration effective to prevent, reduce, or eliminate non-invasive fungus-induced rhinosinusitis. This invention also provides methods and materials for diagnosing non-invasive fungus-induced rhinosinusitis and culturing non-invasive fungus from a mammalian mucus sample as well as specific antifungal formulations and medical devices for treating and preventing non-invasive fungus-induced rhinosinusitis. In addn., the invention provides methods and materials for treating and preventing other non-invasive fungus-induced **mucositis** conditions such as chronic otitis media, chronic colitis, and Crohn's disease. Further, the invention involves methods and materials for treating and preventing chronic asthma symptoms.

IT **79-09-4, Propionic acid**, biological studies **110-91-8D, Morpholine**, derivs. **112-38-9, Undecylenic acid 126-07-8, Griseofulvin 777-11-7, Haloprogin 1397-89-3, Amphotericin B 1400-61-9, Nystatin 2022-85-7**, Flucytosine **2398-96-1, Tolnaftate 7681-93-8, Natamycin 22916-47-8, Miconazole 23593-75-1, Clotrimazole 27220-47-9, Econazole 61318-90-9, Sulconazole 64211-45-6, Oxiconazole 64872-76-0, Butoconazole 65277-42-1, Ketoconazole 65472-88-0, Naftifine 67915-31-5, Terconazole 84625-61-6, Itraconazole 86386-73-4, Fluconazole 110588-57-3, Saperconazole 137234-62-9, Voriconazole**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

L7 ANSWER 3 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:255007 CAPLUS
DOCUMENT NUMBER: 128:316959
TITLE: Nosocomial breakthrough fungemia during

antifungal prophylaxis or empirical antifungal therapy in 41 cancer patients receiving antineoplastic chemotherapy: analysis of etiology risk factors and outcome

AUTHOR(S): Krcmery, V., Jr; Oravcova, E.; Spanik, S.; Mrazova-Studena, M.; Trupl, J.; Kunova, A.; Stopkova-Grey, K.; Kukuckova, E.; Krupova, I.; Demitrovicova, A.; Kralovicova, K.

CORPORATE SOURCE: Department of Medicine, University of Trnava, Trnava, Czech Rep.

SOURCE: J. Antimicrob. Chemother. (1998), 41(3), 373-380
CODEN: JACHDX; ISSN: 0305-7453

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Forty-one episodes of breakthrough fungemia occurring over a 7.5 yr period in the National and St Elizabeth's Cancer Institutes in Bratislava, Slovakia, were analyzed. Five of them occurred during prophylaxis with **fluconazole** (one Torulopsis glabrata, one Hansenula anomala, two Candida krusei and one Candida parapsilosis), ten with **itraconazole** (three Trichosporon pullulans, one Trichosporon beigelii, one Cryptococcus laurentii, three Candida albicans and two T. glabrata), 11 during prophylaxis with **ketoconazole** (one Candida norvegenesis, one C. parapsilosis, one C. krusei, one Candida tropicalis, five C. albicans, one Candida stellatoidea and one C. laurentii) and 15 during empirical therapy with **amphotericin B** (ten C. albicans, two T. beigelii and three Candida lusitaniae). The most frequent risk factors for breakthrough fungemia were neutropenia, previous therapy with multiple antibiotics and recent catheter insertion. Comparing these episodes with 38 non-breakthrough fungemias (appearing at the same institute in the same period) differences in certain risk factors were noted: breakthrough fungemias were more frequently obsd. in patients with acute leukemia (39.0% vs 5.2%, $P < 0.001$), **mucositis** (34.2% vs 13.1%, $P < 0.05$), prophylaxis with quinolones (58.5% vs 15.8%, $P < 0.0001$) and catheter-assocd. infections (29.3% vs 2.6%, $P < 0.003$). In this subgroup overall mortality (36.6% vs 28.8%) or early attributable mortality (22.0% vs 23.6%) were not significantly different.

IT **1397-89-3, Amphotericin B**
65277-42-1, Ketoconazole 84625-61-6,
Itraconazole 86386-73-4, Fluconazole
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(breakthrough fungemia during antifungal treatment in humans with cancer receiving chemotherapy)

L7 ANSWER 4 OF 10 CAPLUS
Searcher : Shears 308-4994

ACCESSION NUMBER: 1997:608865 CAPLUS
DOCUMENT NUMBER: 127:257244
TITLE: Oral administration of short-chain fatty acids reduces the intestinal **mucositis** caused by treatment with Ara-C in mice fed commercial or elemental diets
AUTHOR(S): Ramos, Mariana G.; Bambirra, Eduardo A.; Cara, Denise C.; Vieira, Enio C.; Alvarez-Leite, Jacqueline I.
CORPORATE SOURCE: Departmento de Bioquimica e Imunologia, Instituto de Ciencias Biologicas, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, 30161-970, Brazil
SOURCE: Nutr. Cancer (1997), 28(2), 212-217
CODEN: NUCADQ; ISSN: 0163-5581
PUBLISHER: Lawrence Erlbaum Associates, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Swiss mice fed com. (Nuvital) or elemental (Pepti-Diet Support) diets plus short-chain fatty acids (SCFA) soln. at close to physiol. proportions were treated with the cytostatic drug Ara-C (cytarabine, 3.6 mg/mouse/day) for 2 or 4 days. Histopathol. examn. revealed less damage (atrophy, inflammation, or necrosis) to the small intestine and colon caused by Ara-C when SCFA were administered. Protein and nucleotide concns. in the intestinal mucosa were higher in the group receiving SCFA than in the group receiving a placebo of the same pH and osmolarity. Improvement by the SCFA treatment correlated with an increase in the height of the intestinal villi, with no alterations of the crypts. The no. of intraepithelial lymphocytes was similar to normal values in animals receiving SCFA and Ara-C. When large doses of SCFA were administered, xanthomized enterocytes appeared, suggesting an accumulation of fatty acids in these cells. Thus, oral administration of SCFA at close to physiol. proportions reduces the intestinal inflammation and necrosis caused by Ara-C administration, thus representing a potential factor for the clin. improvement of patients with **mucositis** caused by cancer treatment.

IT **79-09-4**, **Propionic acid**, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(short-chain fatty acids given orally reduce intestinal **mucositis** caused by Ara-C in mice)

L7 ANSWER 5 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:425974 CAPLUS
DOCUMENT NUMBER: 127:106079
TITLE: Regulation of x-ray mediated gene expression with lipoxygenase inhibitors, and use with

radiotherapy
INVENTOR(S): Weichselbaum, Ralph R.; Hallahan, Dennis E.; Kufe, Donald W.
PATENT ASSIGNEE(S): Arch Development Corp., USA; Dana-Farber Cancer Institute
SOURCE: U.S., 21 pp. Cont.-in-part of U.S. Ser. No. 192,107, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5641755	A	19970624	US 1994-278452	19940720
PRIORITY APPLN. INFO.:			US 1994-192107	19940204

AB Treatment of cells with ionizing radiation is assocd. with the prodn. of arachidonic acid. Inhibition of phospholipase A2 abolishes radiation-mediated arachidonate prodn., protein kinase C induction, and tumor necrosis factor gene expression. The addn. of inhibitors of lipoxygenase, e.g. **ketoconazole**, prior to irradn. reduces the expression of of tumor necrosis factor while maintaining the expression of other radiation inducible genes, e.g. Egr-1 and c-jun. In contrast, indomethacin, an inhibitor of cyclooxygenase, enhanced the expression of tumor necrosis factor as well as other radiation inducible genes. The results show that lipoxygenase inhibitors are useful in the treatment of radiation-induced local inflammatory reactions (**mucositis**, etc.) which may be due to the prodn. of cytokines such as TNF. The invention is thus useful in blocking cytokine prodn. following x-ray exposure is to ameliorate the adverse effects of radiotherapy that result from the prodn. of cellular mediators of inflammation and tissue injury.

IT **65277-42-1, Ketoconazole 84625-61-6, Itraconazole 86386-73-4, Fluconazole**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxygenase inhibitors in regulation of x-ray mediated gene expression, and use with radiotherapy)

L7 ANSWER 6 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:377832 CAPLUS
DOCUMENT NUMBER: 127:816
TITLE: Treatment of mucosal disorders in patients receiving radiation therapy or chemotherapy
INVENTOR(S): Bannert, Christian
PATENT ASSIGNEE(S): Bannert, Christian, Germany
SOURCE: Ger. Offen., 5 pp.

CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19541815	A1	19970515	DE 1995-19541815	19951109
WO 9717078	A1	19970515	WO 1996-EP4890	19961107

W: CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: DE 1995-19541815 19951109

AB PEG is useful for removal of thickened mucus from the mouth assocd. with cancer chemotherapy or radiation therapy. PEG is preferably combined with prostaglandins for simultaneous treatment of inflammation (**mucositis**). Thus, an ointment consisting of 250 g PEG-1500, 750 g PEG-300, and 0.01-100 mg% alprostadil or dinoprostone was prepd. for application to the lips or oral mucosa; diln. of this mixt. with water provided a mouth rinse.

IT **1397-89-3, Amphotericin B**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of mucosal disorders in patients receiving radiation therapy or chemotherapy)

L7 ANSWER 7 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:635744 CAPLUS
DOCUMENT NUMBER: 125:265305
TITLE: Phase I study of simultaneous dose escalation and schedule acceleration of cyclophosphamide-doxorubicin-etoposide using granulocyte colony-stimulating factor with or without antimicrobial prophylaxis in patients with small-cell lung cancer
AUTHOR(S): Ardizzoni, A.; Pennucci, M. C.; Danova, M.; Viscoli, C.; Mariani, G. L.; Giorgi, G.; Venturini, M.; Mereu, C.; Scolaro, T.; Rosso, R.
CORPORATE SOURCE: Div. Med. Oncol. I, Ist. Nazionale Ricerca sul Cancro, Genoa, 16132, Italy
SOURCE: Br. J. Cancer (1996), 74(7), 1141-1147
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A phase I study was designed to assess whether dose intensity of an 'accelerated' cyclophosphamide-doxorubicin-etoposide (CDE) regimen plus granulocyte colony-stimulating factor (G-CSF) could be increased further, in an outpatient setting, by escalating the dose

of each single drug of the regimen. Patients with previously untreated small-cell lung cancer (SCLC) received escalating doses of cyclophosphamide (C) 1100-1300 mg m-2 i.v. (i.v.) on day 1, doxorubicin (D) 50-60 mg m-2 i.v. on day 1, etoposide (E) 110-130 mg m-2 i.v. on days 1, 2, 3 and every 14 days for at least three courses. Along with chemotherapy, G-CSF (filgastrim) 5 .mu.g k-1 from day 5 to day 11 was administered s.c. (s.c.) to all patients. Twenty-five patients were enrolled into the study. All patients at the first dose level (C 1100, D 50, E 110 .times. 3) completed three or more cycles at the dose and schedule planned by the protocol and no 'dose-limiting toxicity' (DLT) was seen. At the second dose level (C 1200, D 55, E 120 .times. 3) three out of five patients had a DLT consisting of 'granulocytopenic fever' (GCPF). Another six patients were treated at this dose level with the addn. of ciprofloxacin 500 mg twice a day and only two patients had a DLT [one episode of documented oral candidiasis and one of 'fever of unknown origin' (FUO) with generalized **mucositis**].
Accrual of patients proceeded to the third dose level (C 1300, D 60, E 130 .times. 3) with the prophylactic use of ciprofloxacin. Four out of six patients experienced a DLT consisting of GCPF or documented non-bacterial infection. Accrual of patients at the third dose level was then resumed adding to ciprofloxacin anti-fungal prophylaxis (**fluconazole** 100 mg daily) and anti-viral prophylaxis (acyclovir 800 mg twice a day) from day 5 to 11. Out of five patients threated three experienced a DLT consisting of severe leucopenia and fever or infection. With a simultaneous dose escalation and schedule acceleration it is indeed possible to take max. advantage of G-CSF activity and to increase CDE dose intensity by a factor 1.65-1.80 for a max. of 3-4 courses. The role of antimicrobial prophylaxis in this setting deserves to be investigated further.

L7 ANSWER 8 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:584598 CAPLUS
DOCUMENT NUMBER: 125:265067
TITLE: Benzydamine hydrochloride (Andolex) improves oral mucosal health in the immunocompromised patient
AUTHOR(S): Arendorf, T.; Soloman, C.; Shaikh, A.; Mills, G.
CORPORATE SOURCE: Faculty of Dentistry/WHO Oral Health Collaborating Center, University of Western Cape, S. Afr.
SOURCE: SAMJ (1996), 86(9, Pt. 1), 1136-1137
CODEN: SAMJEJ; ISSN: 0256-9574
DOCUMENT TYPE: Journal
LANGUAGE: Afrikaans
AB Patients with hematol. disorders undergoing chemo- and/or radiotherapy show an increased predisposition to systemic and oral complications. These oral problems may complicate therapy, prolong

hospitalization and cause extreme discomfort to the patient, reducing the quality of life. The oral cavity may also act as a port of entry for systemic infections. The aims of this study were to: (i) evaluate oral complications related to antineoplastic therapy; and (ii) formulate an effective mouth management protocol for these patients. Between Sept. 1992 and August 1995, all patients with hematol. malignancies who were treated as inpatients in the Haematol. Protected Unit at Groote Schuur Hospital, Cape Town, were monitored. Their treatment included chemotherapy or bone marrow transplantation. An examn. form was devised to record and summarize data for each patient. All eligible patients were interviewed and given an oral and peri-oral examn. before receiving antineoplastic treatment. The patients' oral status was assessed twice weekly by a single skilled examiner (dentist) during therapy until their discharge. Diagnoses of oral candidiasis and herpes simplex infection were confirmed by culture. Sixty patients were monitored while following the traditional hospital mouth management regimen. The medications included **nystatin**, chlorhexidine, thymol glycol, hydrogen peroxide and sodium bicarbonate. The hospital regimen was then changed to protocol A (consisting of chlorhexidine and **amphotericin B** lozenges only) and patients were monitored until sample size matched that of the traditional oral regimen (N=60). A further 60 patients were monitored after benzydamine hydrochloride (Andolex; 3M) was added to protocol A (now designated protocol B). Benzdamine hydrochloride is reported to be of benefit in the prevention and management of pain in oral **mucositis** assocd. with radiation therapy. It is a non-steroidal drug that reportedly possesses analgesic, anesthetic, anti-inflammatory and antimicrobial properties. The majority of the 180 patients monitored suffered from acute leukemia (72.2%). Other diagnoses include chronic leukemia, aplastic anemia, multiple myeloma and non-Hodgkin's lymphoma. Of the patients entering the unit 63.0% received chemotherapy followed by bone marrow transplant (25.0%). Other therapies included retinoic acid and antilymphocytic globulin (7%). No significant differences between the three groups were found in respect to type of medical treatment. Oral lesions encountered at baseline examn. included herpetic lesions, angular cheilitis and ulceration. No significant differences between the patient groups were found in respect of the oral complications encountered at baseline examn. The authors found a statistically significant redn. in all the oral lesions combined with the use of protocols A and B (Table I). Only 65.0% of patients developed oral lesions with the use of protocol A, a 10.0% redn. when compared with the hospital oral care regimen. With the use of protocol B, only 48.3% of patients had some form of oral complication, a 26.7% redn. when compared with the hospital regimen. The authors' findings show a statistically significant redn. in the frequency of oral problems assocd. with antineoplastic therapy with the use of protocols A and

B. This improvement may be due to a structured routine and improved oral care. The authors recommended benzdamine hydrochloride as a prophylactic mouth-rinse for immunocompromised patients. This study was supported by the Medical Research Council. The authors acknowledge the assistance of Professor P. Jacobs, Dr M. du Toit, Dr E. Holland, Professor N. Novitsky, and the staff of F4 and E5, Groote Schuur Hospital, Cape Town.

L7 ANSWER 9 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:388947 CAPLUS
DOCUMENT NUMBER: 125:104332
TITLE: Phase II study of polymyxin B, tobramycin, and **clotrimazole** to prevent oral irradiation **mucositis**
AUTHOR(S): Garden, Adam S.; Fleming, Terence; Trissel, Lawrence; Morrison, William H.; Gomez, Dorys; Ang, K. Kian; Peters, Lester J.
CORPORATE SOURCE: M.D. Anderson Cancer Center, University Texas, Houston, TX, 77030, USA
SOURCE: Radiat. Oncol. Invest. (1996), 4(1), 23-26
CODEN: ROINEU; ISSN: 1065-7541
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Colonization of the oral mucosa by gram-neg. organisms and/or fungi is theorized to be an etiol. factor in severe mucosal reactions in patients receiving radiation to treat head and neck cancers. Patients treated with altered fractionation schedules have high rates of confluent **mucositis**, which can be slow to heal and can on occasion disrupt the continuity of the radiation course, with possible detrimental effects on outcome. It has been proposed that antimicrobial agents directed at these organisms can alleviate the severity of the mucosal reactions. We studied the use of a suspension of polymyxin B and tobramycin in conjunction with a **clotrimazole** troche in patients receiving radiotherapy with altered fractionation schedules to the oropharynx or oral cavity. Thirty-seven patients were enrolled in the trial. Radiation doses ranged from 63 to 77 Gy over 5-7 wk. The rate of confluent **mucositis** in the entire group was 84%. This was not significantly different ($P > 0.1$) from a rate of 85% seen in an historical control group of 79 patients treated with our concomitant boost regimen. Possible reasons for the apparent ineffectiveness of this antibacterial-antifungal regimen are discussed.

IT **23593-75-1, Clotrimazole**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase II study of polymyxin B, tobramycin, and **clotrimazole** to prevent oral irradn. **mucositis** in humans)

L7 ANSWER 10 OF 10 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1994:649702 CAPLUS
DOCUMENT NUMBER: 121:249702
TITLE: **Ketoconazole** attenuates radiation-induction of tumor necrosis factor
AUTHOR(S): Hallahan, Dennis E.; Virudachalam, Subbulakshmi; Kufe, Donald W.; Weichselbaum, Ralph R.
CORPORATE SOURCE: Pritzker School Medicine, University Chicago, Chicago, IL, 60637, USA
SOURCE: Int. J. Radiat. Oncol., Biol., Phys. (1994), 29(4), 777-80
CODEN: IOBPD3; ISSN: 0360-3016
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous work has demonstrated that inhibitors of phospholipase A2 attenuate ionizing radiation induced arachidonic acid prodn., protein kinase C activation and prevent subsequent induction of the tumor necrosis factor gene. Because arachidonic acid contributes to radiation-induced tumor necrosis factor expression, we analyzed the effects of agents which alter arachidonate metab. on the regulation of this gene. Phospholipase A2 inhibitors quinacrine, bromphenyl bromide, and pentoxyfylline or the inhibitor of lipoxygenase (**ketoconazole**) or the inhibitor of cyclooxygenase (indomethacin) were added to HL-60 cell cultures 1 h prior to x-irradn. Radiation-induced tumor necrosis factor gene expression was attenuated by each of the phospholipase A2 inhibitors (quinacrine, bromphenyl bromide, and pentoxyfylline). Furthermore, **ketoconazole** attenuated x-ray-induced tumor necrosis factor gene expression. Conversely, indomethacin enhanced tumor necrosis factor expression following irradn. The finding that radiation-induced tumor necrosis factor gene expression was attenuated by **ketoconazole** suggests that the lipoxygenase pathway participates in signal transduction preceding tumor necrosis factor induction. Enhancement of tumor necrosis factor expression by indomethacin following irradn. suggests that prostaglandins produced by cyclooxygenase act as neg. regulators of tumor necrosis factor expression. Inhibitors of tumor necrosis factor induction ameliorate acute and subacute sequelae of radiotherapy. We propose therefore, that **ketoconazole** may reduce acute radiation sequelae such as **mucositis** and esophagitis through a redn. in tumor necrosis factor induction or inhibition of phospholipase A2 in addn. to its antifungal activity.

IT **65277-42-1, Ketoconazole**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ketoconazole** attenuates x-ray induction of tumor necrosis factor)

=> d his 18-; d 1-13 ibib abs
Searcher : Shears 308-4994

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, TOXLIT, TOXLINE, PHIC, PHIN, DRUGU, DRUGB, DRUGLAUNCH' ENTERED AT 16:57:27 ON 10 SEP 1999)
L8 494 S L7
L9 15 S L8 AND INTESTIN?
L10 13 DUP REM L9 (2 DUPLICATES REMOVED)

L10 ANSWER 1 OF 13 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97322577 MEDLINE
DOCUMENT NUMBER: 97322577
TITLE: A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced **mucositis**.
AUTHOR: Okuno S H; Foote R L; Loprinzi C L; Gulavita S; Sloan J A; Earle J; Novotny P J; Burk M; Frank A R
CORPORATE SOURCE: Mayo Clinic, Rochester, Minnesota 55905, USA.
CONTRACT NUMBER: CA-25224 (NCI)
CA-37404 (NCI)
CA-15083 (NCI)
+
SOURCE: CANCER, (1997 Jun 1) 79 (11) 2193-9.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199709
ENTRY WEEK: 19970902
AB BACKGROUND: The objective of this study was to determine whether a nonabsorbable antibiotic lozenge could alleviate radiation-induced oral **mucositis**. METHODS: Patients scheduled to receive radiation therapy to more than one-third of the oral cavity mucosa were selected for the study. After stratification, patients were randomized to receive either a nonabsorbable antibiotic lozenge or a placebo. Both groups were then evaluated for **mucositis** by health care providers and self-report instruments. RESULTS: Fifty-four patients were randomized to receive the antibiotic lozenge and 58 to receive the placebo. There were no substantial differences or trends in **mucositis** scores between the two study arms as measured by the health care providers. However, the mean patient-reported **mucositis** score and the duration of patient-reported Grade 3-4 **mucositis** were both lower in the patients randomized to the antibiotic lozenge arm (P = 0.02 and 0.007, respectively). CONCLUSIONS: This prospective, controlled trial provides evidence to suggest that a nonabsorbable antibiotic lozenge can decrease patient-reported radiation-induced oral

mucositis to a modest degree. Nonetheless, this evidence does not appear to be compelling enough to recommend this treatment as part of standard practice.

L10 ANSWER 2 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-13472 DRUGU T S
TITLE: Phase I study of high dose etoposide phosphatase with filgrastim (G-CSF) in the treatment of advanced refractory malignancies.
AUTHOR: Hainsworth J D; Utley S M; Greco F A
LOCATION: Nashville, Tenn., USA
SOURCE: Invest.New Drugs (15, No. 4, 325-29, 1997) 3 Tab. 19 Ref.
CODEN: INNDDK ISSN: 0167-6997
AVAIL. OF DOC.: Sarah Cannon Cancer Center, 250 25t Avenue North, Suite 412, Nashville, TN 37203, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-13472 DRUGU T S
AB The purpose of this phase I study was to define the maximum tolerated dose of infused etoposide phosphate when used with s.c. G-CSF (filgrastim) in the treatment of 11 patients with advanced refractory malignancies. Toxicity produced by high dose etoposide phosphate included myelosuppression and **mucositis**. Dose-levels which produced dose-limiting toxicity were found. The maximum tolerated dose of etoposide phosphatase in patients given G-CSF was stated. The study concludes that dose-limiting toxicities were myelosuppression and **mucositis**, as with high dose etoposide. Etoposide phosphate can be substituted for etoposide in high dose regimens; due to its greater solubility administration can be more rapid, requires less fluid volume, and is not associated with acidosis.
ABEX Methods 11 Patients (8 male, median age 50-yr) with advanced cancer (of the colon, melanoma, lung, small-cell, nonsmall cell, carcinoid, breast, hepatoma, leiomyosarcoma, non-Hodgkin's lymphoma) refractory to standard treatment were given etoposide phosphate given over 1-2 hrs on 3 consecutive days. The first cohort of patients received a total dose of 1596 mg/sq.m (equivalent to etoposide 1400 mg/sq.m); doses were escalated in subsequent patient cohorts. G-CSF 5 ug/kg was administered subcutaneously from day 4 until the total leukocyte count rose to over 10000/ul. 2 Courses were given at 28 day intervals.Prophylactic antibiotic treatment with ciprofloxacin was also given. Concomitant medication included acyclovir and **fluconazole**. Results Toxicity produced by high dose etoposide phosphate included myelosuppression and **mucositis** . 3 Of 5 patients treated at the 2280 mg/sq.m dose level

(equivalent to etoposide 2000 mg/sq.m) had dose limiting toxicities (grade 4 leukopenia for 7 days, 2 patients; grade 4 **mucositis** plus leukopenia, 1 patient). In addition, median days with severe thrombocytopenia (over 50000/ul) rose to 6 days at this dose. Other toxicity was uncommon. In pretreated patients, the maximum tolerated dose of etoposide phosphate with G-CSF was 1938 mg/sq.m (equivalent to etoposide 1700 mg/sq.m). (SZB)

L10 ANSWER 3 OF 13 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97285107 EMBASE
DOCUMENT NUMBER: 1997285107
TITLE: Oral administration of short-chain fatty acids reduces the **intestinal mucositis** caused by treatment with Ara-C in mice fed commercial or elemental diets.
AUTHOR: Ramos M.G.; Bambirra E.A.; Cara D.C.; Vieira E.C.; Alvarez-Leite J.I.
CORPORATE SOURCE: M.G. Ramos, Depto. de Bioquimica e Imunologia, Universidade Federal de Minas Gerais, 30161-970 Belo Horizonte, MG, Brazil
SOURCE: Nutrition and Cancer, (1997) 28/2 (212-217).
Refs: 17
ISSN: 0163-5581 CODEN: NUCADQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Swiss mice fed commercial or elemental diets and an oral short-chain fatty acid (SCFA) solution or saline were treated with the cytostatic drug Ara-C (cytarabine, 3.6 mg/mouse/day) for two or four days. Histopathological examination revealed less damage (atrophy, inflammation, or necrosis) to the small **intestine** and colon caused by Ara-C when SCFA was administered. Accordingly, protein and nucleotide concentrations in the **intestinal** mucosa were higher in the group receiving SCFA than in the group receiving a placebo of the same pH and osmolarity. Improvement by SCFA treatment was correlated with an increase in the height of the **intestinal** villi, with no alterations of the crypts. Furthermore, the number of intraepithelial lymphocytes was similar to normal values in animals receiving SCFA and Ara-C. When large doses of SCFA were administered, xanthomized enterocytes appeared, suggesting an accumulation of fatty acids in these cells. We conclude that oral administration of SCFA at close to physiological proportions reduces the inflammation and necrosis caused by Ara-C

administration, thus representing a potential factor for the improvement of patients with **mucositis** caused by cancer treatment.

L10 ANSWER 4 OF 13 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96127769 EMBASE
DOCUMENT NUMBER: 1996127769
TITLE: Incidence and prevention of nonhaematological toxicity of high-dose chemotherapy.
AUTHOR: Hoekman K.; Vermorken J.B.
CORPORATE SOURCE: Department of Medical Oncology, Free University Hospital, De Boelelaan 1117,NL-1081 HV Amsterdam, Netherlands
SOURCE: Annals of Medicine, (1996) 28/2 (175-182). ISSN: 0785-3890 CODEN: ANMDEU
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The introduction of the haematopoietic growth factors (HGFs), together with the evolution of techniques to harvest haematopoietic stem cells from the peripheral blood, have greatly facilitated the use of high-dose chemotherapy (HDC). While haematological toxicity of HDC is no longer dose-limiting, damage to other tissues has become more pronounced. In fact, nonhaematological toxicity (NHTOX) is now often dose-limiting in HDC regimens. NHTOX associated with HDC regimens depends on the type and dose of the drugs used, the physical condition and the characteristics of the patients treated and the given comedication. We describe the most important toxic effects of commonly used HDC programmes, such as nausea, vomiting and **mucositis**, neutropaenic fever and sepsis, various major organ toxicities, catheter-associated problems and long-term complications. In addition, we discuss the possibilities of preventing these side-effects and what action to take if they occur.

L10 ANSWER 5 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1996-05656 DRUGU P T S V
TITLE: Treatment of advanced colorectal cancer with high-dose intensity folinic acid and 5-fluorouracil plus supportive care.
AUTHOR: Petrioli R; Lorenzi M; Aquino A; Marsili S; Frediani B; Palazzuoli V; Marzocca G; Botta G; Tani F; Martino A De; Testi W; Setacci C; Salvestrini F; Sando D De; Bovenga S; Mariani L; Mancini S; Tanzini G; Armenio S;

Marinello E; Francini G
CORPORATE SOURCE: Univ.Siena
LOCATION: Siena; Grosseto, It.
SOURCE: Eur.J.Cancer (31, No. 12, 2105-08, 1995) 1 Fig. 3 Tab. 16 Ref.
CODEN: EJCAEL ISSN: 0964-1947
AVAIL. OF DOC.: Cattedra di Oncologia Medica, Universita di Siena, Nuovo Policlinico Le Scotte, Viale Bracci 11, 53100 Siena, Italy. (G.F.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1996-05656 DRUGU P T S V
AB High-dose intensity i.v. folinic acid (FA) and i.v. 5-fluorouracil (FU) was more effective than conventional FU treatment in a randomized study of 185 patients with advanced colorectal cancer. Side-effects were mild and slightly more pronounced in the FA/FU group than in the FU only group. Side-effects included stomatitis, diarrhea, nausea, vomiting, dermatosis, leukopenia, phlebitis, **mucositis**, neutropenia and alopecia. Supportive treatment included p.o. loperamide for diarrhea, hyoscine for **intestinal** colic, p.o. morphine for abdominal pain, vitamin C, carnitine derivatives, ademethionine, **Nystatin** and Bacillus subtilis. Accelerated FU/FU treatment achieves a higher response rate and longer survival than conventional FU alone in patients with colorectal cancer.

ABEX Methods 185 Patients (41-72 yr) were randomized to receive FA 200 mg/sq.m and FU 400 mg/sq.m for 5 days every 3 wk or FU 400 mg/sq.m for 5 days every 4 wk. Treatment was planted for 12 cycles or until disease progression. Patients who achieved CR received 3 further consolidation cycles. Supportive care in both groups 3 days before and 5 days after chemotherapy included i.v. 1000 ml normal saline, 1 g vitamin C, 20 mg carnitine derivatives, 200 mg ademethionine, **Nystatin** 10000 U and p.o. Bacillus subtilis. Loperamide 2-6 mg was used for severe diarrhea, hyoscine for **intestinal** colic and morphine for other abdominal pain. Results The FA/FU groups received a median of 8.5 cycles and the FU group 7 cycles. 167 Patients were evaluable.The overall response rate was 33.3% for the FA/FU group and 18.6% for FU only. In the FA/FU group, 4 patients achieved CR and 23 achieved PR; 35 patients had stable disease and 19 progressive disease. In the FU group, 3 achieved CR, 13 PR, 41 had stable disease and 29 progressive disease. The median response duration was 9 mth in the FA/FU group and 5.5 mth in the FU group. Median survival was 13.5 mth in the FA/FU group and 7.5 mth in the FU group. The side-effects of treatments were mild and slightly more pronounced in the FA/FU group than in the FU group. Stomatitis and diarrhea were the main side-effects. (E35/KS)

L10 ANSWER 6 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1993-55872 DRUGU T S E
TITLE: In Search of an Optimal Regimen for Elderly Patients With Advanced-Stage Diffuse Large-cell Lymphoma: Results of a Phase II Study of P/DOCE Chemotherapy.
AUTHOR: O'Reilly S E; Connors J M; Howdle S; Hoskins P; Klasa R; Klimo P
LOCATION: Vancouver, British Columbia, Canada
SOURCE: J.Clin.Oncol. (11, No. 11, 2250-57, 1993) 7 Fig. 4 Tab. 18 Ref.
CODEN: JCONDN ISSN: 0732-183X
AVAIL. OF DOC.: Department of Medical Oncology, British Columbia Cancer Agency, 600 W 10th Ave., Vancouver, BC, V5Z 4E6, Canada. (7 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1993-55872 DRUGU T S E
AB I.v. epirubicin (EP) (or i.v. doxorubicin (DX), i.v. vincristine (VC), i.v. cyclophosphamide (CP) (i.v. and p.o. etoposide (ET) and p.o. prednisone (PD) (P/DOCE) led to a 45% survival rate in a phase II trial of 63 elderly patients with advanced diffuse large-cell lymphoma.Side-effects included **mucositis** (worse with DX), dysesthesias and motor neuropathy (with VC), granulo- and thrombocytopenia, neutropenic fever and fatal cardiopathy, GI bleeding, septicemia, infectious bowel ischemia and aspiration pneumonia. Cotrimoxazole trimethoprim + sulfamethoxazole), cimetidine and **ketoconazole** (all p.o.) were given. The outcome with P/DOCE was similar to that seen previously in 72 patients with low-dose DX, CP, VC, bleomycin (BM) and PD (LD-ACOB-B) or ET, DX, BM and PD (VABE).
ABEX Methods 63 Previously untreated patients (31 male, aged 65-85 yr, median age 75 yr) with advanced-stage diffuse large-cell lymphoma received P/DOCE for 8 wk. Patients received i.v. EP at 50 mg/sq.m for wk 1, 2, 7 and 8, i.v. VC at 1.2 mg/sq.m i.v. CP at 300 mg/sq.m for wk 1, 4 and 7, i.v. ET at 50 mg/sq.m on day 1 and p.o. ET at 100 mg/sq.m on days 2, 3, 4 and 5 for wk 4, p.o. PD at 50 mg/day for 10 days starting in wk 1, 4 and 7. The 1st 22/63 patients received i.v. DX at 40 mg/sq.m on wk 1, 2, 7 and 8, but severe **mucositis** led to EP being given instead of DX. Prophylactic p.o. cotrimoxazole (b.i.d.), p.o. **ketoconazole** (200 mg/day x 10) and p.o. cimetidine (600 mg b.i.d.) were given. 5/63 Patients received radiotherapy. Results 39/63 Patients had a CR, 18/63 a PR and 6/63 no response. There were 5/63 toxic deaths due to a cardiovascular event, GI bleeding, septicemia, infectious bowel ischemia and aspiration pneumonia. The actuarial projected 4-yr overall survival rate was 45% and the failure-free

survival rate was 41%. Follow-up was 10-52 mth (median 33 mth for living patients). Grade 3-4 **mucositis** occurred in 18% of DX- and 7% of EP-treated patients. 69% Of patients had granulocyte count of below 1000 million/l and 8% a platelet count of less than 50000 million/l. 20% Of patients had severe febrile neutropenia or other infectious complications. Adverse prognostic factors included age over 60 yr, ECOG performance status of 2 or worse, increased LDH levels, stage III or IV disease and 2 or more extranodal disease sites. (E61/MB)

L10 ANSWER 7 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1992-41385 DRUGU T M P S
TITLE: Phase I and Pharmacokinetic Study of Rhizoxin.
AUTHOR: Bissett D; Graham M A; Setanoians A; Chadwick G A; Wilson P; Koier I
LOCATION: Glasgow, United Kingdom; Amsterdam, Netherlands
SOURCE: Cancer Res. (52, No. 10, 2894-98, 1992) 2 Fig. 7 Tab. 6 Ref.
CODEN: CNREA8 ISSN: 0008-5472
AVAIL. OF DOC.: CRC Department of Medical Oncology, University of Glasgow, Alexander Stone Building, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, Scotland. (11 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AN 1992-41385 DRUGU T M P S
AB The effects of i.v. bolus rhizoxin were assessed in a Phase I study in 24 patients with solid tumors (breast, colorectal, gallbladder, sarcoma, pancreas, lung, melanoma, mesothelioma or unknown primary), previously treated with radiotherapy and/or chemotherapy (including vincristine (VC)). Side-effects included alopecia, injection site and tumor site pain, nausea/emesis, phlebitis, peripheral neuropathy, **mucositis** (refractory to **nystatin** (NY)), diarrhea, neutropenia, thrombocytopenia, septicemia, pyrexia, anemia and urticarial rash. 2 Patients with breast cancer had minor responses. Plasma-concentration time-profiles showed considerable intersubject variation. RH has some clinical activity and is recommended for Phase II study.
ABEX Methods 24 Patients (33-70 yr-old, median 55, 9 men) with refractory solid tumors received i.v. bolus injection of RH over 5 min, once every 3 wk. Dose was escalated from 0.8 to 1.6, 2 and 2.6 mg/sq.m. Plasma RH levels were measured by HPLC. Results 60 Courses of RH were given. Dose was reduced in 2 patients at 1.6 mg/sq.m due to myelotoxicity and in 2 patients at 2.6 mg/sq.m due to **mucositis**. Other side- effects were neutropenia, thrombocytopenia, diarrhea, **mucositis** (not prevented by NY), septicemia, pyrexia (in 1 patient each), nausea, emesis,

sensory peripheral neuropathy (digital paresthesia and numbness), alopecia, injection site discomfort, mild phlebitis, moderately severe tumor site pain, anemia and urticaria. Many patients had less toxicity after the 2nd and later courses than the 1st. Minor responses occurred in 2 patients with advanced local recurrent breast cancer, treated at 1.6 and 2.6 mg/sq.m respectively. Response lasted 4-12 wk. 7 Other patients had stable disease and 14 had progression of disease. RH was undetectable in plasma of patients receiving 0.8 and 1.6 mg/sq.m and was only detected for up to 10 min following 2 mg/sq.m injection in 3 patients. Peak plasma drug level 2 min after treatment at 2 mg/sq.m was 16-43 ng/ml. In 1 patient, plasma levels were sufficiently high to allow fitting of pharmacokinetic results to a biexponential model. Trapezoidal AUC was 0.96 ug/ml.min, compared with values in the other patients between 0.29 and 0.59 ug/ml.min at a dose of 2.6 mg/sq.m. (E67/TOB)

L10 ANSWER 8 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1992-34168 DRUGU T S
TITLE: Gut Protection by Cyclophosphamide "Priming" in Patients Receiving High-Dose Melphalan - Effect of Drug Scheduling.
AUTHOR: Mansi J; Ellis E; Viner C; Mundy J; Smith T; Millar J
LOCATION: Sutton, United Kingdom
SOURCE: Cancer Chemother.Pharmacol. (30, No. 2, 149-51, 1992) 1 . Fig. 1 Tab. 10 Ref.
CODEN: CCPHDZ ISSN: 0344-5704
AVAIL. OF DOC.: Section of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, England. (9 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1992-34168 DRUGU T S
AB The amount of p.o. 51Cr-EDTA excreted was similar in 32 myeloma patients receiving melphalan (ML) with an autologous bone marrow transplant and randomly assigned to receive i.v. cyclophosphamide (CY) at 5, 7 or 9 days before ML. The duration of **mucositis** and diarrhea was equivalent for each group. All patients received high-dose i.v. methylprednisolone, antifungal agents including **nystatin** and amphotericin, cimetidine or ranitidine and allopurinol (all p.o.). The timing of the priming CY treatment is not critical, it can be given between 5 and 9 days before high-dose ML.
ABEX Methods 32 Myeloma patients received ML (200 mg/sq.m) with autologous bone marrow transplant; 13 patients received CY (400 mg/sq.m) 5 days before ML, 9 at 7 and 10 at 9 days before ML. All patients had 51Cr-EDTA (4 MBq) for the absorption test to measure **intestinal** permeability and methylprednisolone (1.5 g daily for 5 days); prophylactic antifungal agents included

nystatin (1 ml, q.i.d.) and amphotericin (10 mg, q.i.d.). Cimetidine (400 mg) or ranitidine (300 mg) and allopurinol (300 mg) were given daily for 7 days. Results The median % 51Cr-EDTA excretion in groups given CY 5, 7 or 9 days before ML was 9.1, 7.1 and 7.7%, respectively. There was no difference between the groups in the number of patients developing severe **mucositis** or diarrhea. The % patients with grade 2 **mucositis** with CY priming at day 5, 7 or 9 before ML were 61, 60 and 80%; respective values with grade 3/4 **mucositis** were 31, 10 and 50%, those with grade 2 diarrhea were 92, 70 and 80% and with grade 3/4 diarrhea 54, 20 and 70%. (K20/SAB)

L10 ANSWER 9 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1990-26350 DRUGU T S
TITLE: Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) After High-Dose Melphalan in Patients with Advanced Colon Cancer.
AUTHOR: Steward W P; Scarffe J H; Dirix L Y; Chang J; Radford J A; Bonnem E
CORPORATE SOURCE: Schering-Plough
LOCATION: Manchester, United Kingdom; Antwerp, Belgium; Kenilworth, New Jersey, United States
SOURCE: Br.J.Cancer (61, No. 5, 749-54, 1990) 3 Fig. 5 Tab. 31 Ref.
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Beatson Oncology Center, Western Infirmary, Glasgow G11 6 NT, Scotland. (7 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1990-26350 DRUGU T S
AB In a phase 1/11 study, continuous infusion of i.v. granulocyte-macrophage colony stimulating factor (GM-CSF, Schering-Plough, Sandoz) increased peripheral granulocyte counts, was not associated with toxicity, and reduced the duration of neutropenia and thrombocytopenia induced by high-dose i.v. melphalan (ME) (+ frusemide) treatment of 9 patients with advanced carcinoma of the colon. 1 Complete (CR) and 2 partial (PR) remissions were obtained. Other ME-associated side effects were alopecia, nausea and vomiting, diarrhea, oral **mucositis**, fever, infection, reduced Hb, and hemorrhage. 1 Treatment-related death occurred in a patient who developed oliguria while receiving piperacillin, vancomycin, netilmicin and **amphotericin-B**.
ABEX Methods 9 Patients (5 male, aged 33-66 yr, median 47 yr) with advanced metastatic cancer of the colon, recieved GM-CSF (3 ug/kg/day, escalating to 10 ug/kg/day after 10 days if target WBC was not achieved). 7 Days after achieving target WBC count (50 x

10 power 9/l) and discontinuing GM-CSF, ME (120 mg/sq.m) was given as a short i.v. infusion with hydration and frusemide, and 8 hr later GM-CSF was restarted and continued for more than 1 wk after re-achieving target WBC count. Results 1 Patient achieved target WBC at 3 ug/kg/day, but the other 5 required escalation to 10 ug/kg/day. No GM-CSF associated toxicity was observed, but ME related toxicity comprised total alopecia, nausea and vomiting, diarrhea, oral **mucositis**, fever, infection, reduced Hb, leukopenia, granulcotyopenia, thrombocytopenia, and hemorrhage. Median times to severe neutropenia and thrombocytopenia were 6 and 9 days, respectively, and the median duration of neutropenia and thrombocytopenia were 14 and 10 days, respectively. All patients required intensive support with a mediation duration of inpatient stay of 24 days. A single treatment related death was attributed to renal failure. 1 CR and 2 PR were achieved, but median duration of response was only 10 wk. (W111/AL)

L10 ANSWER 10 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1990-40945 DRUGU T S
TITLE: Toxic Complications in Bone Marrow Recipients.
AUTHOR: Lyubimova L S; Savchenko V G
LOCATION: Moscow, Russia
SOURCE: Ter.Arkh. (62, No. 7, 120-27, 1990) 1 Tab. 10 Ref.
CODEN: TEARAI ISSN: 0040-3660
AVAIL. OF DOC.: VGNTs, Ministry of Health of the USSR, Moscow, U.S.S.R.
LANGUAGE: Russian
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1990-40945 DRUGU T S
AB The occurrence and control of toxic effects in patients receiving bone marrow transplants are reviewed, with particular reference to side effects of cytostatic therapy used for preparation of patients. The major problems during preparation result from the toxicity of drugs such as cyclophosphamide (CPX) and myelosan (MY), and of irradiation; they include nausea and vomiting, fever, **mucositis** and conjunctivitis, lesions of **intestinal** peristalsis, cystitis, etc.; infections resulting from immune suppression can also be major problems. Treatment is decided individually, and has prophylactic and therapeutic components. 2 Illustrative case histories are described.
ABEX The major problem with bone marrow transplantation is early death due to toxicity during preparation, infection developing on a background of agranulocytosis, and acute secondary disease. Usual preparative regimes consist of CPX (60 mg/kg), for 2 days followed by whole body irradiation (2 Gy b.i.d. for 3 days), followed by MY (4 mg/kg for 4 days) and CPX (60 mg/kg for 2 days); some centers use even more drastic regimes. Resulting toxic effects often include cystitis, hepatitis, occlusion of hepatic veins,

cardiotoxicity, **intestinal** syndrome, anorexia, **mucositis** and nausea and vomiting. For example, patient S (male, 27 yr) with acute myeloblastic leukemia, was prepared with CPX and irradiation, which induced moderate dyspepsia, cystitis, **intestinal** syndrome, slightly elevated bilirubin and mild **mucositis**; on day 10 after transplantation there was pain on touching soft tissues of the leg and mouth, which developed into severe necrotic oral rash. Neck edema developed on days 14-16, and S died suddenly on day 15 with cardiac arrest. Autopsy showed no focal myocardial changes. Another example is given: patient K (female, 27 yr) with acute myeloblastic leukemia and a history of cardiac dysrrhythmia was prepared with MY and CPX, along with i.v. insulin, allopurinol, dopamine, droperidol, pipolphen, meprobamate, lasix, **nystatin** and phenoptin; K also received cyclosporin A (ciclosporin) and methotrexate. Slight hepatotoxicity occurred on day 5, and cystitis and renal changes on days 7-9. Cardiotoxicity with ventricular asystoles appeared on day 4, and responded to panangin and riboxin. Sudden hypotension on day 6 responded to lignocaine. (W149/AK)

L10 ANSWER 11 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1988-06903 DRUGU T M S
TITLE: The Combination of a Third Generation Cephalosporin (Cefotaxime or Ceftazidime) and a New Quinolone (Pefloxacine) in the Treatment of Febrile Episodes in Neutropenic Patients.
AUTHOR: Guy H; Caillot D; Solary E; Bielefeld P; Portier H; Kazmierczak A
LOCATION: Dijon, France
SOURCE: Presse Med. (16, No. 43, 2172-75, 1987) 3 Tab. 9 Ref.
CODEN: PRMEAI ISSN: 0755-4982
AVAIL. OF DOC.: Centre Hospitalier Universitaire de Dijon, 2, bd Marechal de Lattre-de-Tassigny, BP 1542, F 21034 Dijon Cedex, France.
LANGUAGE: French
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1988-06903 DRUGU T M S
AB Pefloxacin (PF) with cefotaxime (CF) or ceftazidime (CZ), all i.v., were effective against febrile episodes due to Staph. epidermidis, Staph. aureus, E. coli and Ps. aeruginosa in 33 neutropenic leukemia patients. Ps. maltophila, Ps. putida and Ps. aeruginosa were resistant and infections with e.g. Strept. faecium refractory to PF, CF or CZ responded to piperacillin (PP), vancomycin (VM), netilmicin (NL), amikacin (AK), erythromycin (EM), **amphotericin B** (AB) p.o. or **nystatin** (NS) p.o.; results were complicated by **mucositis** due to rubidazone and i.v. aracytine. Tolerance was good with evidence of

slight hepatotoxicity. (congress).

ABEX Methods 33 Neutropenic patients received CF and PF (17 patients, aged 23-75, mean 53.7 yr) and 16 (aged 18-75, mean 54.8 yr) received CZ and PF to resolve 37 febrile events. PF was given i.v. at 800 mg/day, CF i.v. at 4 g/day and CZ at 6 g/day in glucose. They also received p.o. AB at 4 g/day and 3 x 10 power 6 U NS. Results An 86% immediate success rate was achieved (32/37 cases) and a 2nd febrile episode occurred in 11 cases. For CF and PF there was 18 successes. CF and PF resistant strains of Staph. epidermidis responded to VM and NL combination. **Mucositis** due to rubidazone (200 mg/sq.m for 4 days) and aracytine (300 mg/sq.m for 7 days) against acute myeloid or lymphoid leukemia complicated interpretation. With CZ and PF there were 14 successes and failures resolved after treatment with VM and AK or finally after VM, EM, i.v. AB and i.v. AC. Isolates included Staph. epidermidis, Staph. aureus, E. coli, Ps. aeruginosa. Most isolates of aerobic **intestinal** flora (Ps. maltophila, Ps. putida and Ps. aeruginosa) were resistant to CF, CZ and PF. A superinfection with Strept. faecium resolved after PP, AK and VM. Tolerance was satisfactory with no withdrawals. There was evidence of slight hepatotoxicity although 4/6 patients had received aracytine and anthracyclines. (E4/JS) (Association d'Une Cephalosporine de Troisieme Generation (Cefotaxime ou Ceftazidime) et d'Une Nouvelle Quinolone (Pefloxacine) dans le Traitement des Episodes Febriles des Malades Neutropeniques (37 cas).)

L10 ANSWER 12 OF 13 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1984-35092 DRUGU M T
TITLE: Can Antibacterial Therapy Be Discontinued in Persistently Febrile Granulocytopenic Cancer Patients. (Question).
AUTHOR: Joshi J H; Schimpff S C; Tenney J H; Newman K A; Jongh C A de
LOCATION: Baltimore, Maryland, United States
SOURCE: Am.J.Med. (76, No. 3, 450-57, 1984) 1 Fig. 4 Tab. 22 Ref.
CODEN: AJMEAZ ISSN: 0002-9343
AVAIL. OF DOC.: University of Maryland Cancer Center, University of Maryland Hospital, 22 South Greene Street, Baltimore, Maryland 21201, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1984-35092 DRUGU M T
AB Discontinuation of initial (empiric) antibacterial therapy proved successful in 8/16 cancer patients with persistent fever and granulocytopenia in the absence of demonstrable infection (out of a total of 429 febrile, granulocytopenic episodes), with

reinstitution of antibacterial medication being required in the other 8 cases (6 of these were additionally started on i.v. **amphotericin B** for presumed fungal pneumonia).

Basic antibacterial therapy consisted of amikacin in combination with ticarcillin, moxalactam, piperacillin or azlocillin. In 14/16 patients, concurrent p.o. prophylaxis was given, using **nystatin** in combination with nalidixic acid, gentamicin-vancomycin or sulfamethoxazole-trimethoprim. Among 3 who died, 1 patient had necropsy-confirmed, chemotherapy -associated (methotrexate) pneumotoxicity.

ABEX Patients (13 male, 3 female; aged 20-66, mean 40, yr) included 10 with acute nonlymphocytic leukemia (4 in remission, 1 in relapse), 1 with acute lymphocytic leukemia (in relapse), 1 with chronic granulocytic leukemia (in blast crisis) and 3 with progressive lymphoma. In these 16 cases, both fever and granulocytopenia were still present at about 4 days after initiation of initial antibacterial therapy, although no infectious process could be identified at that time. The initial regimen was, therefore, discontinued after an average of 4.8 (median 5.0) days. Such discontinuation of medication was found to be appropriate in 8 patients, who exhibited no evidence of infection during the next 2 wk (at least). However, reinstitution of antibacterial therapy was deemed advisable in the other 8 patients, with an infection being microbiologically documented in 1 case (bacterial pneumonia) and being clinically apparent in 6 cases (2 of cellulitis, 2 of **mucositis** with or without concomitant pharyngitis and 2 of pneumonitis; however, 1 of the pneumonitis cases was later found to originate from methotrexate pneumotoxicity). In 6 of these patients, empiric **amphotericin B** therapy was necessitated by the suspected development of candidial or aspergillal pneumonia as well as mucosal and **intestinal** candidiasis. Reinstitution of antibacterial therapy was required more often among patients with relapsed leukemia or lymphoma and/or a likelihood of continued profound granulocytopenia (counts below 100/ul) than among patients lacking these pathological features.

L10 ANSWER 13 OF 13 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 81130961 EMBASE
DOCUMENT NUMBER: 1981130961
TITLE: Pseudomembraneous enterocolitis: Mechanism of restoring floral homeostasis.
AUTHOR: Bowden Jr. T.A.; Mansberger Jr. A.R.; Lykins L.E.
CORPORATE SOURCE: Dept. Surg., Sect. Gastroint. Surg., Med. Coll. Georgia, Augusta, Ga. 30912, United States
SOURCE: American Surgeon, (1981) 47/4 (178-183).
CODEN: AMSUAW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
Searcher : Shears 308-4994